Ulcerative Colitis with Liver Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. AARONSON*: The patient, a 24-year-old male graduate student, had a history of abdominal pain, bloody diarrhea and weight loss beginning ten years before the present admission to hospital. Eight years before admission a diagnosis of ulcerative colitis was made after barium enema and sigmoidoscopic examination. The symptoms abated until four years ago when the patient was put in hospital for recurrence of diarrhea and weight loss of 30 pounds. Three months before the present admission, he was found to be anemic. Physical examination revealed enlargement of the liver. On sigmoidoscopy the colon was noted to be edematous, friable and ulcerated. Serum bilirubin and alkaline phosphatase levels were elevated. One month before the present admission he was put in hospital because of injury in a fall from a bicycle. On examination there, fever, splenomegaly and elevation of serum alkaline phosphatase were noted. He denied arthritis, dermatitis, iritis, jaundice or exposure to toxic chemicals. He also denied any drug administration or exposure to patients with infectious diseases. It was then that he was transferred to this hospital for further studies.

The blood pressure was 135/65 mm of mercury, the pulse 88 and regular and temperature 38°C (100.4°F). The skin was not icteric and no lymph nodes were palpated. The liver, felt 1 cm below the right costal margin, was firm and nontender. The spleen was tender and was felt 3 cm below the left costal margin. The remainder of the abdominal examination was within normal limits.

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Hemoglobin was 10.1 gm per 100 ml, packed cell volume 35 per cent, sedimentation rate 28 mm in one hour, leukocyte count within normal limits, with 8 per cent eosinophiles. Serum cholesterol was 202 mg and serum bilirubin was 1.6 mg per 100 ml (direct 0.6 mg), alkaline phosphatase 22 Shinowara-Jones-Reinhardt units, bromsulphthalein retention 25 per cent, serum albumin 2.7 gm and serum globulin 3.4 gm per 100 ml, and serum 5-nucleotidase 21 units (normal less than 1.5 units). The prothrombin time varied between 40 and 60 per cent.

Sigmoidoscopic examination revealed friable, bleeding rectal mucosa and no masses. Bone marrow examination showed absence of iron stores. A needle biopsy of the liver was interpreted as within normal limits.

The patient was treated with prednisone by mouth, 15 mg per day, hydrocortisone, 100 mg in oil by enema every evening, and sulfasoxazole 2 gm three times a day. He was discharged with a diagnosis of ulcerative colitis and probable pericholangitis.

DR. RUSSELL*[1]: There are several interesting x-ray findings in this patient. The initial chest film showed streaky densities in both apices. What appears to be a small effusion on the left, which showed up well in the oblique projection, might also have been pleural thickening. Barium enema demonstrated a large spleen displacing the splenic flexure medially and anteriorly. The barium enema

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studies were otherwise unremarkable. There was no evidence of ulceration of the colon at this time, and the mucosal pattern appeared normal. A persistently narrowed area, although changing somewhat in shape, was demonstrated in the region of the recto-sigmoid junction by multiple spot films. Oral cholecystograms on two successive days showed poor visualization of the normal gallbladder. No gallstones were seen.

Hepatic Disease as a Complication

DR. SMITH*[2]: Actually there are many aspects of ulcerative colitis which could be presented, but we decided this morning to give major emphasis to one of the complications of ulcerative colitis—namely, hepatic disease. We have asked Dr. Howard Shapiro to open this discussion. We would particularly be interested in knowing how frequently this complication occurs and how important it is in the prognosis of the disease.

DR. SHAPIRO*[3]: That is a large order. I think that in our present state of knowledge, the description will be primarily phenomenological.

Briefly, this 24-year-old man had a ten-year history of very mild ulcerative colitis. He had one severe exascerbation before there was any suspicion of liver disease. The liver disease was really discovered by serendipity. The patient was asymptomatic but the physician was rather bothered by a low hemoglobin, and investigation of that problem ensued. When the patient was first studied, he had conjugated hyperbilirubinemia and an elevated alkaline phosphatase. Again he remained asymptomatic until the accident which precipitated his hospital admission. We were able to confirm the elevation of alkaline phosphatase. We were fairly certain that this was due to liver disease because there was pronounced elevation in the serum 5-nucleotidase, a test which is more specific for obstructive liver disease since it is not affected by bone disease. He also had bromsulphthalein retention of 25 per cent, which probably accounts for the poor visualization of the gallbladder. Results of the other tests of hepatic function were quite normal. Of interest to me was the fact that the blood cholesterol was normal. There will be further comment on this finding later. Initially he had a febrile course and later became afebrile on no specific therapy. He was treated vigorously with rectal instillations of steroids, oral sulfonamides and systemic steroids, and was then discharged. The dramatic thing about this patient is not the clinical course, rather it is the abnormalities noted on chemical studies of the liver that pique our curiosity. I am sure that the patient would be just as well off and just as happy if he had never entered the hospital nor had the investigations carried out.

We have known for a number of years that liver disease has been associated with ulcerative colitis. The initial studies on the relationship between liver disease and ulcerative colitis were done mostly on necropsy material supplemented with infrequent data on surgical biopsy of the liver. These early studies,[6] in the late 1940's and early 1950's, on the association of liver disease and ulcerative colitis were necessarily biased by the manner in which these specimens of liver were obtained for examination. In patients with ulcerative colitis and liver disease, a 50 per cent incidence of fatty liver was found in the autopsy series. The fattiness of the liver was considered secondary to malnutrition, protein loss through the rectum and a generalized toxic state. Generally the degree of fattiness found at autopsy in ulcerative colitis parallels the severity of the disease. It is a nonspecific finding. In these early studies the incidence of cirrhosis was 7 per cent, primarily postnecrotic rather than Laennec's type. Considering the incidence of fatty liver, Laennec's cirrhosis is quite rare in ulcerative colitis. Biliary cirrhosis was noted infrequently. These early studies shed little light on the pathogenesis of liver disease in ulcerative colitis.

In 1952, the first communication on needle biopsy of the liver in a series of patients with ulcerative colitis appeared from the Mayo Clinic.[2] Kleckner and coworkers, the authors of the report, were the first to consider pericholangitis as a distinct entity in ulcerative colitis. In 32 cases of liver disease and ulcerative colitis, biopsy demonstrated fatty liver in 13, cirrhosis in six and pericholangitis in six. These investigators felt that the cause of the pericholangitis in these patients was secondary to bacteria and toxic products reaching the liver through the portal vein. In 1959 similar observations were reported in Australia by Rankin and coworkers[7] who for the first time characterized pericholangitis as a lesion in ulcerative colitis. They too considered it secondary to portal bacteremia. In 1959 Rankin and his coworkers treated six patients with broad spectrum antibiotics. Initially they noted promising results in that these

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patients did have some improvement of liver function and less frequent bouts of fever, jaundice and pruritus. Later they themselves came to doubt that the tetracyclines really have much to offer in the treatment of pericholangitis associated with ulcerative colitis.

More definitive observations were made by Mistilis[3,4] and his associates in Australia who published two excellent papers in 1965 on the clinical aspects, pathogenesis, pathology and some etiologic consideration of pericholangitis. Their work had been carried out carefully over a 15-year period. Among 450 patients with ulcerative colitis (this was their clinic population) 28 also had pericholangitis. The patient presented today fits well the clinical description of those patients. Thirteen of the 28 patients were completely asymptomatic. The disease came to light because of enlargement of the liver, and all had elevated alkaline phosphatase determinations. None of the asymptomatic patients had any other stigmata of liver disease.

The next largest group of patients had episodic, cholestatic jaundice. These patients had episodic attacks of jaundice and pruritus associated with elevation of the alkaline phosphatase level. These episodes would vary from weeks to months but they were never very dramatic. There were no pre-icteric symptoms, and there were long asymptomatic periods between these episodes of jaundice and pruritus.

The third group of patients had cholangiolytic attacks. They had bouts of pruritus, fever, abdominal pain and mild toxemia associated with some liver tenderness. Icterus was variable. Again, the alkaline phosphatase level was always elevated. These attacks were rather sudden in onset without pre-icteric symptoms, and lasted for days to weeks. There were long asymptomatic periods between these attacks, some as long as four to twelve years.

There were many patients who had cholangitic attacks with long asymptomatic periods and then a cholestatic episode as well. The clinical differentiation among these three groups is really a stationary one; at any one time, one can differentiate among these three groups, but longitudinally any one patient may have all three types of pericholangitis in association with ulcerative colitis. The ulcerative colitis in all of the patients that Mistilis described was very mild. Such is the case in the young man presented today. In patients that did have severe episodes of ulcerative colitis, these episodes usually antedated the diagnosis of liver disease. The colitis was usually left-sided; universal involvement was unusual. Mistilis and his coworkers noted in their cases something that was not observed in today's patient—that the extracolonic manifestations of ulcerative colitis were quite frequent. A number of their patients had transient arthralgia. Three had chronic active hepatitis in association with a positive lupus erythematosus phenomenon.

In all of their patients the alkaline phosphatase level was elevated. Hypercholesterolemia was usual but by no means universal, and an increase in bromsulphthalein retention was common. The transaminase determinations, if they were elevated at all, were very slightly elevated to a level less than 200 units. The serum electrophorectic pattern was frequently normal but occasionally hypergammaglobulinemia was present. The flocculation tests were all normal.

Three Categories of Pericholangitis

In their description of the pathologic features of pericholangitis, Mistilis and his coworkers divided the cases into three categories: Acute, subacute and chronic. The acute phase is characterized by cellular infiltration in the portal tracts, some swelling and edema of the finer biliary structures, and generally some dilitation and prominence of the lymphatic structures within the portal tracts. In the subacute phase there is a pronounced decrease in the cellular infiltration and edema of the portal tracts, and a general increase in the connective tissue and in fibroblastic proliferation in the portal tracts. There is often some hyaline change in the ductal walls.

As this progresses into the chronic phase, there is a pronounced decrease in the inflammatory cell response in the periportal areas. Indeed, what seems to happen is a shift of the zone of inflammatory cell response out of the portal triads and into the junctional zone between the portal tracts and the adjoining parenchymal cells. In the chronic phase, it can resemble chronic active hepatitis because there is actual hepatic cell necrosis and inflammation in the periportal areas. In this chronic phase there is a decided increase of periportal and circumductal fibrosis, leading to a stellate appearance of the portal triads. Lymphangectasia is present. Because of the shift of the junctional inflammatory zone to the liver parenchyma, there is piecemeal necrosis of hepatic parenchyma which suggests frank cirrhosis. The

chronic phase of the pericholangitis can resemble postnecrosic cirrhosis or chronic active hepatitis, and indeed six of their twenty-eight patients had postnecrotic cirrhosis and eight had chronic active hepatitis. The chronic active hepatitis was almost always associated with hypergammaglobulinemia, and in three cases the result of a test for lupus erythematosus was positive.

It is interesting that the Mistilis group repeatedly performed liver biopsy on their patients over a period of 15 years and found no false sampling. In cases of metastatic carcinoma our own experience in liver biopsy suggests a positive diagnosis in 60 to 70 per cent. Similar findings occur in sarcoidosis as well. Frequently in cirrhosis the specimen is from a perfectly normal area and the cirrhotic area missed. That they found liver biopsy diagnostic in all cases is quite remarkable.

Mistilis expressed belief that the progression of acute to subacute to chronic pericholangitis is inevitable.[5] In all cases, there was slow but definite progression of disease. Four patients had colectomy, five were given antibiotic therapy over long periods and several were treated with a low dose of corticosteroids. Despite these various modes of therapy the liver disease progressed.

The Possible Role of Bacterial Infection

There were several factors that I have mentioned in the description of this disease that pique one's curiosity about its genesis. I don't think that anyone who has dealt with this disease feels that he can make definite statements about the cause, but the findings of perilymphangitis and periphlebitis and intense portal inflammatory responses do lend support to the possibility that bacterial infection has a role in triggering the illness. The portal blood is usually sterile but portal bacteremia has been demonstrated in many patients with ulcerative colitis. The onset of this pericholangitis might be associated with an acute infectious process. However the fact that it does not respond to antibiotic therapy or to total colectomy suggests that once the disease is established in the portal tract it is self-perpetuating.

These conjectures about a self-perpetuating liver disease triggered by an acute infection are reminiscent of chronic active hepatitis, or so-called lupoid hepatitis, which is considered by most observers to be an autoimmune disease. In chronic active hepatitis it has been suggested that the virus particle damages the live cell, which somehow induces it to act as an antigen against itself, leading to a self-perpetuating mechanism that is triggered perhaps by acute viral infection. In the pericholangitis of ulcerative colitis, I suppose one could also consider an autoimmune phenomenon to explain the progressive nature of this disease. If this is the case, one might expect to see hypergammaglobulinemia more commonly. One would also expect a better response to corticosteroid therapy.

Varying Rate of Progression

DR. SMITH: Thank you very much, Dr. Shapiro. The most surprising thing to me in your discussion was the prognosis. I was not aware that a patient such as we have seen today with relatively minor alterations of liver function would almost invariably have progressive attacks leading to severe hepatic derangement. What would you expect the time course to be?

DR. SHAPIRO: I have mentioned that the course is invariably progressive, but that the time that it takes for the progression to occur is quite variable. Some patients in Mistilis' series have gone 15 years between attacks of cholangitis, some have had a much more rapid progression. Since the liver biopsy in today's patient has been interpreted as normal and since he is relatively asymptomatic now, he may show his first signs of progression 15, 20 or 25 years from now. In that sense, life itself is a progressive disease.

DR. SMITH: Dr. Carbone, has this been your experience in ulcerative colitis?

DR. CARBONE*[4]: Yes. We have several patients who have had relative stability of ulcerative colitis for 15 years. During this period of time, three patients of this group have developed cirrhosis and progressive liver failure. The terminal stage of their liver disease is portal cirrhosis. However, at varying times one will find pericholangitis and a significant incidence of sclerosing cholangitis.

Treatment of patients with ulcerative colitis and liver disease has been disappointing with respect to the progressive changes in the liver. Even though these patients have been treated continuously with steroids, either systemically or by retention enemas and continuous sulfonamides, the natural history of the liver disease has been progressive. This is in spite of excellent control of colitis and, in many instances, a complete reversal

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of the inflammatory lesion of the colon.

There is reason to believe that the combination of ulcerative colitis and liver disease may be a different disease than idiopathic ulcerative colitis. These patients, as a group, tend to have a milder form of colitis and more extracolonic manifestations of the disease. They lack the usual response to colectomy and oftentimes the colitis becomes apparent after the liver disease has been documented.

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